A remarkable legacy: Ian MacKenzie and the ARI

Mark Hogarth

Ian McKenzie (MD, PhD, FRACP, FRACPath) has recently retired as the Founding Director of The Austin Research Institute, the culmination of 40 years of clinical practice and medical research. Ian’s long and illustrious career has been built on high quality basic research and its translation into applied useful therapeutics, centred largely around the immunology of transplantation, cancer, infection and inflammation. Indeed, there would be few better examples of the “bench to bedside” approach to research that is all the more remarkable for its breadth and consistent quality across such a diversity of research activities. The outcomes are reflected in Ian’s 650 publications and the Institute’s 120 granted patents over 26 families. Those of Ian’s peers who know his prodigious organisational skills and his capacity for work, his clear thinking and dedication to research and his qualities of perseverance, integrity and most of all his appreciation for the potential of others based on ability rather than status, understand how it was possible for Ian to be a highly active researcher in many areas, the ASI President (1984), TSANZ President (1991 - 1992) and founding Institute director.

Ian’s values, qualities and capabilities are evident in all aspects of his life and can be traced back to his early days as a competitive swimmer. As is often the case, achievement in elite sport often translates into achievement in other walks of life. At the age of five, Ian joined the Brunswick Swimming Club which, according to the local newspaper, was “in the hope it would develop his rather frail body”. (It must have worked!) By his late teens and early twenties, Ian had won a number of Victorian freestyle, backstroke and butterfly championships, was ranked number one in the world in butterfly and was the Victorian team captain on a number of occasions. Michael Hunt who was also a Victorian champion swimmer (later becoming famous as the referee on World Championship Wrestling and who has since gone on to establish a major successful interstate business) recalled that Ian was the most organised and dedicated swimmer of his peers. He knew exactly what training schedules he was doing and had planned his training and events 12 months ahead which in the late ’50s/early ’60s was highly unusual for amateur sports. He was succeeding at his medical studies at the same time, receiving several Honours.

One of the major characteristics of Ian’s career, apparent in his time as a champion swimmer, is his ability to mentor others. Ian’s swimming peers remember him as extremely generous with his time for others, despite his heavy commitments to his medical studies and his own swimming, and for being highly reliable, dependable and honest. Ian took on the position as coach in the swimming association’s Training Panel, which was designed to develop the younger swimmers. The elite swimmers of the day acknowledged Ian’s mentoring as being the single essential

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2003 Membership Renewal enclosed

Please complete Update Questionnaire and return with renewal form and payment to the ASI Secretariat as soon as possible. Please indicate on renewal whether you wish to have your contact details published in the 2003 Membership Directory.

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Website
The ASI web site (www.wehi.edu.au/collegiate/ASI/) has been fully remodelled and updated. New services include:
- Downloadable forms for ASI awards,
- Positions vacant pages,
- Jobs wanted pages,
- Upcoming conferences listings,
as well as a plethora of links to sites of immunological interest at home and abroad. If you’d like your lab home pages linked to the site, would like to advertise a job or conference, or have a favourite immunology-related site that doesn’t currently appear on the ASI site, please e-mail Judy Greer at j.greer@medicine.uq.edu.au

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Rituximab from IDEC pharmaceuticals currently is one of the hottest biotech drugs on the market, earning already $1 billion (US) in annual sales only a few years after release in the US. Why mention that here? Bear with me for a moment.

You will have seen already Mark Hogarth’s tribute to Ian McKenzie upon his retirement as Director of the Austin Research Institute in Melbourne. Mark’s article is broad ranging and gives an excellent insight into the qualities that form the backbone of Ian’s remarkable success. While reading Mark’s article I was surprised to learn that Ian McKenzie was a number one world rated swimmer. I’m not surprised in the sense that I can’t believe Ian was capable of such an achievement, rather that many scientists have another life, before or parallel with their scientific career, that usually goes unnoticed. Despite attempts to categorise and parody the scientist in the popular imagination, as a group they seem to be as diverse and mixed in skills as any other slice of society. The source of scientific ability is one of the great mysteries of life, along with artistic temperament. It seems we are as likely to find athletes, singers, antique collectors, optimists and naysayers as you are in any other group. Apart from a few famous examples, skill at science seems not to be inherited and there is no particular trait that seems to be essential apart from the obvious ones of being innately curious and persistent in approaching a problem. This diversity of skills brought to science by each individual is very enriching for the community, and one of the joys of working in science.

Given that ability at science is inherited in an unpredictable way it is particularly important the skills and methods of the excellent and most successful are noted and passed down from generation of scientist to the next. There is little formal way of doing this except by the apprenticeship PhD system and the circulation of stories and examples. Often a way of thinking or approaching a problem is communicated in some witty or succinct form. Kevin Lafferty would persistently challenge anyone with his famous “whats your f….ing hypothesis”, or on hearing some dubious piece of student logic would say dismissively “Yeah well, if your Aunt Mary had balls she would be your Uncle Harry”. In this regard I often wonder about Burnet and how many of his methods and sayings, attitudes and approaches are still circulating in our scientific community and contributing to the successful pursuit of science here. How could we tell? Did he invent or adopt favourite aphorisms or sayings that helped summarise his opinions?

I would like to hear from any reader who worked with Burnet directly who might provide some light on the Burnet method and whether there were any such aphorisms that we might find still in circulation. In fact, let’s not restrict the search to Burnet - I would like to collect a set of Australian and New Zealand ‘aphorisms’ and publish them here occasionally and store then as a repository of our history. Let me know if you have any favourites, and their source.

But to return to Mark’s article on Ian McKenzie, you will also notice a few remarks that may require teasing out. Mark mentions a decision in the early ’90s not to support a CRC in monoclonal antibody development and therapy for cancer in Melbourne. Mark recalls the application failed on the basis the Committee thought that there was no future for monoclonal antibodies as therapeutics”. Which in turn brings me back to the opening of this essay. You may have guessed by now that Rituximab is a monoclonal antibody, against a common garden variety B cell marker CD20 that is effective in many cases of lymphoma. According to IDEC Pharmaceuticals, they have a slew of promising monoclonal antibodies currently in development. So in a remarkably short time the CRC committee have proved to be spectacularly wrong in their expert assessment. Do we search out the constitution of the committee that told Ian there was no future in monoclonal antibody therapy of cancer and give them demotions for a job poorly done? While individuals are mercilessly evaluated on performance, no such retrospective is visited on committees, in my experience. Increasingly our science is run and influenced by committees which serve an important purpose but can also defer and dilute responsibility and may have the opposite effect of their intention. I know committees are well intentioned and do excellent work, however, we must never imagine they can do the job of predicting the future. Only the visionary individual is capable of that, and even then maybe once in a lifetime.

This brings the year to a close, thanks to all who contributed articles to our newsletter and hope to hear from you all again next year as we continue to pursue our common fellowship and bond that is Australian and New Zealand immunology.

Phil Hodgkin
component of their success. Ian’s capacity to mentor, or take on the interests of younger people, was clearly seen in his research life where he has been responsible very directly for the research career development of 138 post-graduate students – PhD, MD, MS, Masters and so on. A large number of these have come from non-traditional backgrounds – nurses, school leavers, other people who have entered medical research from different professions, e.g., the building industry – a large number of whom have ultimately become NH&MRC Research Fellows, Wellcome Fellows, Hughes Fellows, QEII, NIH and so on or have become attorneys and company executives.

Ian’s research career is of course tied to his early life as a physician (MB BS 1961, MD 1966) with a number of accolades and prizes in his medical training. His PhD at the University of Melbourne (1970) was based on the antibody mediated destruction of transplants, a research theme that was to recur throughout his career and culminated in the mid 1990s with his observations jointly with Mauro Sandrin that the target for antibody induced destruction of xenografts was a carbohydrate epitope. This of course paved the way for a myriad of strategies around engineering animal organs as potential organ donors.

His work at the Royal Melbourne Hospital was followed by six years research in the USA at the Massachusetts General Hospital with Paul Russell and Henry Winn and at the Jackson Laboratories in Bar Harbour, Maine. It was at the Jackson Laboratories, though, that he teamed up with George Snell (later to receive a Nobel Prize for Medicine) not only to explore aspects of transplantation genetics using the remarkable collection of recombinant inbred and congenic mouse strains but to develop work that formed one of the cornerstones of modern immunology: the development of reliable polyclonal antibodies reacting with lymphocyte antigens for the identification and characterisation of cell surface receptors and the manipulation of leukocyte subsets – the so called Ly antigens later to become the CD antigens. Ian and George Snell, simultaneously with Lloyd Old (now Director of the Ludwig Institute) and Ted Boyse, described the first mouse lymphocyte antigens detected by antibodies. This work showed that the selective expression of surface molecules defined subsets of lymphocytes. Since this original work there have been over 109,000 publications identifying, studying, targeting and manipulating these molecules and the cells that bear them, for both basic science and applied use. Where would we immunologists be without the CD45+ memory cell, the CD38+ stem cell, the CD2+ T cell or the CD11b dendritic cell?!

Ian’s return in 1974 to Australia to the Austin Hospital’s Department of Medicine led him to expand his transplantation and Ly/CD cell surface molecule work and apply this by being one of the principal developers of monoclonal antibodies in Australia. Not only did this basic research into cell surface proteins expand but it led to the development of diagnostic tests for ovarian and breast cancer and ultimately to the first human trials of monoclonal antibody:drug conjugates and antibody:radioisotope conjugates in cancer. In addition to the host of new Ly and CD antigens, the first altered cancer cell antigens were also described. His laboratory’s first monoclonal antibodies were produced as early as 1978 [by Hogarth and others, Editor’s insert] and indeed many of the people who set up monoclonal antibody laboratories in this country were trained by Ian.

Transplantation work at the Austin initially involved the description of the function of Class I and Class II molecules in the mouse. The important studies here were firstly the demonstration that mutation of Class I molecules altered antigen presentation, using the bm and other mouse strains. Although forgotten now, in 1974/5 the demonstration by Doherty and Zinkernagel of Class I virus antigen presentation was fiercely argued: i.e., were these observations due to Class I molecules or to associated molecules encoded by linked genes? The demonstration by Ian that a single mutation simultaneously altered both a histocompatibility locus (H-2) and antigen presentation clearly demonstrated that the Doherty and Zinkernagel phenomenon was due to a single, Class I H-2 molecule. Secondly, a number of disparate immunological phenomena were linked to an indeterminate number of putative Ir genes, such as the mixed lymphocyte reaction (MLR), IA antibodies, rapid graft rejection (H-2) and immune regulation (suppression): but were these 4 separate loci or were they the same? Ian’s description of the bm12 mutant mouse with colleagues in the USA (Henry Kohn and Roger Melvold) where all these functions were simultaneously altered (Class II mutation) demonstrated they were one phenomenon and the variously named Ir genes, LAD, H-2I and I-A were essentially abandoned as they were the same. Transplantation mechanisms were also tackled using Jacques Miller’s thymectomy method to investigate effector cells in mouse skin allograft rejection, and a distinct role for Ly+2 (now CD4) T cells, distinct from Ly2 (CD8) cytotoxic T cells, was identified during Bruce Loveland’s PhD project research.

A move to the Parkville campus at the University of Melbourne in the Pathology school (1981) led to the development of the Research Centre for Cancer & Transplantation, one of the 10 Special Research Centres (then called Centres of Excellence which ultimately evolved into the CRC program). This centre was based around the use of monoclonal antibodies for the diagnosis and treatment of cancer, the isolation of cell surface molecules for protein sequencing and gene cloning, for the modification of transplant rejection processes and for analysis and description of functional lymphocyte subsets in immunity. This period at the Centre (1981-1991) led to the first cloning of immunologically relevant genes in the Ly and human CD antigen families including CD4, CD8, Fc receptors, and complement regulatory proteins. It was also characterised by some of the first immunologically related genes to be patented in Australia. The development of cancer diagnostic assays, which eventually were to be used in the diagnosis of breast and ovarian cancer, and the first use of monoclonal antibodies in human trials for the treatment of disease initiated a stronger human immunology program. Indeed, Ian with Geoff Pietersz pioneered the conjugation of radioisotopes, drugs and toxins to antibodies through the then unique combination of organic chemistry and protein chemistry and indicates Ian’s eye for the application of new technologies to the treatment of human disease. In the mid 1980s these were radically new approaches to disease diagnosis and treatment and many of these principles we today take for granted.
The price of “excellence” was that the NH&MRC froze all of Ian’s grants and banned applications for new ones; the ARC declared all such research ineligible for ARC support - so in a rare moment NH&MRC and ARC shared the same vision! Finally, in a classic example of the Australian approach to excellence, it was decided to terminate the Special Research Centre program, transfer those monies from the Prime Minister’s Department into the ARC and make medical research applications ineligible. Caught up in this Interdepartmental bureaucratic vortex, the future of the group despite all its achievements was bleak. Fortunately, the opportunity to establish the Austin Research Institute (ARI) arose and Ian and a group of researchers and students moved in 1991 into the renovated 19th century Kronheimer Building at the Austin & Repatriation Medical Centre in Heidelberg.

The decade of development at the Austin Research Institute has seen a greater emphasis on the translation of basic research to patients with the development of potential cancer vaccine therapies, which are now about to enter a Phase II clinical trial; the discovery of the target of xenograft rejection and the engineering of complement regulator expressing transgenic pigs; the X-ray crystallographic studies of human Fc receptors (the first structures of their type leading to novel functional studies); a series of platform technologies for vaccine development in infectious disease and the development of a suite of biotech enterprises to commercialise the Institute’s intellectual property.

In reflecting on the last ten years of Ian’s career, the ARI is clearly a testament to his vision, drive and love of medical research. The Institute and its various predecessors under Ian’s directorship had the longest running, largest and arguably the most successful NH&MRC program grant. It attracted substantial foreign grant support, grew a portfolio of 128 patents in 28 families (all Australian intellectual property), developed a range of potential therapeutics and has grown in number from that original 20 staff to over 100. Gordon Ada, one of Australia’s great immunologists, commented that a remarkable feature of Ian’s achievements is to have taken less than a decade to build such a successful research institute in Melbourne that reliably achieves in such a wide range of disciplines in the face of some of the most intense competition for the limited research pie. Ian’s career has been characterised by a visionary approach to research. The introduction and development of monoclonal antibodies when they were in their embryonic phase globally must rank as a major achievement. Indeed it was so visionary that attempts to establish a CRC in the early 1990s around the use of monoclonal antibodies failed on the basis the Committee thought that there was no future for monoclonal antibodies as therapeutics! Ian was never interested in the latest fashionable monoclonal antibodies as therapeutics! Ian’s fundamental belief has always been that if the experiment was well controlled and clear and did not fit the dogma, the dogma and not the experiment was wrong. The controversy around the mucin cancer vaccine antigen is diffusing now that the once immutable rules of peptide:MHC anchoring have proven much too limited for reality and Vasso Apostolopolous with Ian Wilson (Scripps Institute) have produced definitive crystallographic evidence of MHC bound non-canonical peptides, showing the original experimental data were correct. A new set of peptide binding rules has emerged along with a flurry of publications from a surprising number of groups! The vaccine developed from these studies will soon be in a Phase II clinical immunotherapy trial.

Finally, Ian has genuinely provided exemplary research opportunities for others, especially amongst developing investigators. Perhaps what Ian is not best known for is the extent to which he provides support behind the scenes. He has actively promoted other people, nominated many for awards and I am sure many recipients have never been aware of this. It is perhaps one of the mysteries of Australian research why Ian has never been admitted to the august bodies such as the Academy of Sciences in Australia.
In reference to your touching article on the long search for the appropriately phallic Bursa Limerick Trophy: there is another ASI relic which is an even greater treasure.

In the 1970s, Professor Bede Morris was still maintaining that B and T lymphocytes were only distinguished by being the first and last letters of “Bullshit”. Of course, history has shown him to be wrong, but at the time he made a hilarious film to prove his point. It started, as I remember, with two identical electron micrographs of lymphocytes, one labelled “B” and the other “T”. This, he said, showed conclusively there was no difference between them. He then proposed to search for the bursa. India ink was dropped on a bird’s bottom, which responded by taking it in enthusiastically by a process that looked like reverse peristalsis. Then came the rectal examination of an emu. Of course this involved anaesthetising the hapless bird. It was the recovery process which had ‘em rolling in the aisles. If you haven’t seen an emu coming out of anaesthetic and staggering away on legs flailing… Of course an Animal Experimentation Ethics Committee would never permit such an experiment these days, but that was Bede for you.*

This film was shown at the ASI meeting in December 1973, then in 1974 at the International Congress of Immunology in Brighton. The Brits first looked worried about the Science, then shocked and unsure of themselves as it descended into ribaldry. The Australians were helpless with laughter.

So who knows where this film is? Can we find a copy to be shown, next time in Canberra maybe, to a new generation of immunologists who believe there have always been two populations of lymphocytes?

* I have no doubt that anaesthetising the emu was part of a perfectly legitimate experiment, carried out for some valid reason quite unrelated to Bede’s film.

Christina Cheers
Department of Microbiology and Immunology
University of Melbourne

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A new search – Bede’s emu

Ian’s research interests continue and he is actively developing research programs that are aligned with the need to develop new treatments for cancer and transplantation. He maintains an active interest in his sailing and swimming (three shoulder reconstructions later), in his friends and regrettably, in the Collingwood Football Club. In his typical way, Ian refused to have any fuss associated with his retirement, content to accept a signed football jumper from the Collingwood Football Club and the warm recognition of his peers and younger colleagues who know him well and realise what an outstanding and visionary scientist he has been and continues to be.

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Christina Cheers
Department of Microbiology and Immunology
University of Melbourne
**ASI Councillors’ News**

**Victorian News**

Recently we had annual IgV meeting at Beechworth, for the first time after several years successively running at Mt. Buffalo. The Scientific Program was once again strong and the new venue proved very popular with half the attendance from new people. Special thanks to all the invited speakers, particularly Professor Ian McKenzie for his contribution to the meeting. It is great for our students to get to interact with so many of our leading immunologists in this informal setting and this year students represented half the attendees. Winners of student prizes included Mark Chong, Morag Milton, Melissa Martyn, Judith Field, and Marie-Claude Gouel – congratulations to you all. Again, thank you to all the attendees who supported the meeting and to the members of IgV committee who worked behind the scenes to make the meeting another success. Your ASI funds are well spent by supporting the running of our annual meeting.

We are now looking for feedback concerning the venue and time of year for our 2003 IgV meeting. A questionnaire handed out at this year’s meeting in Beechworth asked attendees to compare Mt Buffalo and Beechworth. Most people rated the 2002 meeting very good and value for money. There was an evenly split vote for Beechworth versus Mt Buffalo as a venue, with some nostalgic voting from previous Mt Buffalo attendees. Everyone attending was happy to go to another IgV outside of Melbourne. So what about you folk who have failed to make one of our recent meetings? We are really looking to increase our attendance from WEHI and Melbourne University immunologists. What can we do to make this a meeting you can not afford to miss?

The IgV committee is happy to receive your feedback: m.smyth@pmci.unimelb.edu.au

Mark Smyth
Councillor

**S.A./N.T. News**

Most of the South Australian activities centred on visiting speakers. August was quite busy with Mark Smyth from the Peter McCallum Cancer Institute coming over from Melbourne and giving two excellent talks, then Nilabh Shastri from Berkley University stopped by in Adelaide before he went on to the BIG meeting in Queensland and we were delighted to hear about his findings on antigen processing. Bernadette Scott from the Monash Institute of Reproduction & Development in Melbourne and Richard Lake from the Tumour Immunology Group, WA Institute for Medical Research in Perth gave a combined seminar on the “Biology and Immune Response to Mesothelioma”.

Tom Braciale from the Beirne B. Carter Centre for Immunology Research at the University of Virginia came over to Adelaide in October after his attendance at the Fenner Conference on Vaccines in Canberra to give us a great talk and some insight in his work on T-Lymphocytes Function in RSV Infection.

We are also delighted that Pat Holt from the Division of Cell Biology at the TVW Telethon Institute for Child Health Research in Perth gave the annual student meeting of the SA Branch will be held in December. Students (members and non-members) who wish to present and compete for the annual prize (valued at $200) should submit the title of their talk and a short CV to me by the end of November. Members are encouraged to come along and hear about the research interests of our local post-graduate students at this important Branch function.

Finally, congratulations to all those South Australian ASI members who were successful with their NH&MRC grant applications!

Su Heinzl
Councillor

**Queensland News**

Queensland ASI’s activities had a little rest during the last couple of months (still digesting the successful annual BIG meeting in August), but gearing up now with new strength for the upcoming ASI conference in Brisbane. The conference committee, which consists of representatives of the major immunology research institutes in Brisbane, has entered the final lap in their organization frenzy and is adding the finishing touches to a beautiful conference program (which you can judge, soon). A recent immunological highlight was the QIMR institute seminar given by Prof. Thomas Braciale, director of the Beirne B. Carter Center for Immunology Research in Charlottesville USA. Tom gave a gripping example how the G-protein of Respiratory Syncitia Virus, RSV, can fool the immune system by deviating a potentially effective RSV-specific CD8 T cell response into oblivion, and how these mechanisms can contribute to the high morbidity in the young and elderly.

Norbert Kienzle
Councillor

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**Sustaining Membership**

ASI Inc acknowledges the support of the following sustaining members:
- Bioquest Limited
- Dynal Pty Ltd

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ASI Inc. Newsletter December 2002
**W.A. News**

WA ASI has enjoyed some great immunological presentations from invited interstate speakers over the past few months or so. On 2 October, Assoc. Prof. Frank Carbone from the Department of Microbiology and Immunology at the University of Melbourne gave an excellent seminar titled: “Antigen presenting cells and cytotoxic T cells in herpes simplex virus infection” which was well attended and generated significant interest. ASI WA thanks Invitrogen who provided support for this seminar. During his 2-day visit to Perth, Frank held numerous discussions with a range of local immunology groups and in some cases this led to new collaborations.

On 28 October, Prof. Anne Kelso from the Cooperative Research Centre for Vaccine Technology at The Queensland Institute of Medical Research presented a fascinating seminar on recent work from her group in a talk entitled: “The secret life of CTL: unexpected diversity in phenotype and function”. Anne also took time out of her busy schedule to do a tour of Perth labs, which was greatly appreciated.

Plans for Perth ASI 2003 are moving along well and we hope to have an exciting and stimulating meeting lined up for you next year that you will all want to attend. The theme for the meeting will be “Immune regulation, infectious disease and tumour control”. The meeting will be held on the beautiful University of Western Australia campus from 7–11 December. Prof. Rolf Zinkernagel (Institute of Experimental Immunology, Zurich, Switzerland) has made a commitment to attend the meeting as Burnet Orator.

Other major international speakers who will be attending the meeting include:
- Dr David Cosman (Amgen, Seattle, USA)
- Prof. Ruslan Medzhitov (Yale University, USA)
- Prof. Giorgio Trinchieri (Schering-Plough, France)
- Prof. Jonathon Yewdell (NIH, Bethesda, USA)
- Prof. Laurence Zitvogel (Institut Gustave Roussy, France)

We look forward to seeing you all in sunny Perth in December 2003.

Finally, I would to thank local ASI members for their support and interest during my enjoyable 2-year term as WA ASI Councillor and would like to wish the incoming Councillor a successful and enjoyable term.

Tony Scalzo
Councillor

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**N.Z. News**

A scientific consortium, including Drs Mike Berridge and Jacquie Harper from the Malaghan Institute have won an NZ$8.5 million contract to look for extracts from marine sponges and New Zealand plants that have anti-inflammatory properties that may be useful as therapeutics for immune-mediated diseases such as asthma and arthritis.

Dr Patrizia Stoitzner from the Department of Dermatology at the University of Innsbruck in Austria is currently on study leave in Christchurch Clinical School. Patti is working in the laboratory of Drs Judy McKenzie and Alex McLellan. She has a busy schedule organised to visit each centre before Christmas to present her work on skin dendritic cells and their migration. The title of her talk is “Tracking leukocyte movement from the skin into the lymph nodes”.

Thought for the month: Basic science is like shooting an arrow in the air and where it lands, painting a target. – H. Adkins.

Best joke of the month: On wall in ladies room: “My husband follows me everywhere...” Written just below it: “I do not!”

Glenn Buchan
Councillor

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**Contributions sought for the ASI Newsletter**

**Deadline for the next issue**

**1st February 2003**

Please email your contributions to the Secretariat by the above date.

asi@21century.com.au